mand a large concentration of all types of patients, as well as the clinical, pathological, and biochemical departments of the medical schools. This will assure correlation of research with all existing methods of treatnent, and will give opportunity for proper evaluation of results and determination of patients for whom new methods are indicated.

The present trend of cancer research is toward the field of biochemistry. The work with heavy metals at the tumor clinic of the Jefferson Hospital illustrates the efforts in this direction. Another valuable research is that at the Lankenau Hospital on the relation of the sulphydryl radical to cell division. Experimental work on growth restraint and palliation from various endocrine extracts is being pursued both in this country and in Italy. All of these methods should receive a final determination of their value, but they must be considered in the early experimental stage at the present time.

CANCER A PUBLIC HEALTH PROBLEM

There are medical economic considerations which make it important for the profession in California to give serious thought to cancer therapy. Cancer is rapidly coming to be considered a public health problem. Because of the large mortality, which is rapidly increasing in spite of our popular education and improved methods of therapy, many public health authorities consider that the cancer problem is one which should be subject to state control. In 1929 the legislature of Massachusetts directed the State Board of Health to establish cancer clinics throughout the state, and to establish a cancer hospital which should be open to the entire population. This action was taken with little regard to the will or desire of the medical profession. Fortunately the program was developed with the advice and help of the leaders in medicine in Massachusetts, and the clinics were located only with the consent and active coöperation of the county medical society in each locality. The program has proven of immeasurable value to the medical profession as well as to the public. Nevertheless this is state medicine. However, other states will follow this lead. Such a program of state development and state control will undoubtedly be proposed in California. It behooves the California Medical Association and the county medical societies to anticipate such action with serious, active consideration. We should plan well our cancer program so that we may lead and direct legislation in this work as we hope to do along other medical economic lines.

SUMMARY

Summing up this presentation, may I not say that cancer therapy is a challenge to the medical profession in California.

The responsibility of future cancer mortality statistics rests primarily upon the education of the general practitioner and the family physician. With him lies the possibility of the prevention of a large percentage of cases of cancer, and it is he who must detect the suspicious lesion or symptom of early cancer while it is still curable.

We must make early diagnosis and adequate treatment accessible throughout the state. To accomplish this, the California profession should solidly support the program of the American College of Surgeons as outlined by its Committee on Malignant Disease.

We should immediately provide at least two large cancer institutes, equipped for treatment, research, and education of the profession. These two institutes should have the active assistance of the related departments in our four medical schools and should coöperate with the cancer groups in every large center of the state.

We should be prepared to advise and direct legislation and public health activity in the prevention and treatment of cancer, so that they may serve the best interests of the public as well as the medical profession.

Let us tell the public the truth about cancer—that the only hope of cure lies in the early recognition and immediate destruction of the growth. This will continue to be the truth whatever the outcome of our future research.

Let us recognize the fact that cancer diagnosis and cancer treatment are group problems and are no longer the function of the individual physician, or of any one specialty.

Let us organize cancer groups throughout California that we may bring to the public early, accurate diagnosis and efficient treatment.

While we strive for palliation in the thousands of patients who have advanced cancer, let us place equal emphasis upon the education of the medical profession concerning early diagnosis and treatment and upon scientific cancer research. Then the mortality rate of cancer in California will cease to increase and will begin to decrease even as the mortality rate has decreased in tuberculosis.

510 Medico-Dental Building.

SUSCEPTIBILITY TO TUMORS—SOME OF THE FACTORS GOVERNING THE SAME*

By CHARLES L. CONNOR, M. D.
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DISCUSSION *by Howard A. Ball, M. D., Los Angeles; H. J. Ullmann, M. D., Santa Barbara; W. T. Cummins, M. D., San Francisco.*

IT is well known to those working with experimental tumors that certain factors govern transplantation or inoculation from one animal to another. I say transplantation *or* inoculation, because tumors may in general be divided into transplantable and inoculable tumors. The first require living cells for successful transmission to host animals; the second may be transmitted by the filtered juice or extract, or by the dried, presumably dead, tissue. There are certain laws, however, which govern both types in much the

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same degree. It is the purpose of this paper to point out these factors, to draw an analogy between the behavior of experimental tumors and human tumors, and to show how some of the factors may be altered by experimental methods.

ADAPTATION OF TUMORS TO ANIMALS AND OF ANIMALS TO TUMORS

There is considerable evidence that there is a racial, probably hereditary factor in the susceptibility of animals to specific tumors. This applies particularly to genera and species, but may apply to strains or varieties within species. When the Rous fibrosarcoma was first found in a Barred Plymouth Rock chicken, it could be transmitted only to Barred Plymouth Rocks. Later it was found to "take" in a certain proportion of Rhode Island Reds, and still later in white Leghorns. When first inoculated into a strange variety the "takes" may be small in number. Later, by successive inoculations through the same strain the percentage of successful transplants approaches a hundred. Furthermore, this tumor has now passed through so many generations that inoculation into an entirely new strain of chickens is usually successful. This seems to be an adaptation of the cells of the tumor, or the virus, or both, to a variety of strains of animals within the same species.

That also corollary adaptation can be produced seems to be well established. By breeding animals which are only moderately susceptible, proportionately, to tumors, a strain may be produced in which practically every individual is susceptible to tumor; or an immune strain may be produced. The Slye strain of mice, and the Buffalo strain are well known examples. It seems, therefore, that not only cells may undergo an adaptive change by biological evolution, but that animals may be made to adapt themselves, or to inherit a susceptibility to the transplantation of certain cells of a related animal.

By other more artificial means animals and cells have been made to adapt themselves to one another. Sticker [1] was able to transmit a dog tumor to a fox. Fujinami and Hatano [2] have successfully transmitted a chicken tumor to ducks. Murphy [3] transmitted a sarcoma of mice to rats by x-raying the spleen of the host animals, but when the spleen regenerated, the inoculated tumors regressed. It is likely that the removal of the ovaries or testes of animals may influence the transmission of tumors to unrelated animals. Once this mutual adaptation is accomplished each succeeding generation of the tumor shows an increasing proportion of takes until a maximum percentage; usually between 85 and 100, is reached. That this adaptation, both as to tumors and as to animals, is in the nature of an inheritable character there can be no doubt.

TRANSPLANTATION OF NORMAL TISSUES AND TUMOR GROWTHS

Artificial tumors may be produced in animals. By "artificial tumors" I mean masses of growing tissue which feed upon the host but are not actually a part of the host's anatomy, and which may be the result of experimental transplantation. Some of the laws which govern the transplantation of adult normal tissues to normal animals are known. Transplantation from one species to another is practically impossible; from one animal to another of the same species rather difficult; from an animal to another portion of the same animal less difficult. Here, too, the type of tissue makes a difference, as only tissue which ordinarily has a great ability to regenerate when partly destroyed can be successfully transplanted—thyroid, for instance, as opposed to striped muscle which regenerates practically not at all.

Embryonic tissues may be more readily transplanted than adult. Carrell [4] produced tumors in chickens by transplanting chick embryos to adults along with a weak solution of arsenic trioxid. White [5] repeated this, and transmitted the tumors for several generations. Such tumors are teratomas at first. However, the most viable tissue only, mesenchymal connective tissue, continues to grow, and a tumor resembling an embryonal fibrosarcoma results. Here again, as in the case of spontaneous transmissible tumors, species specificity, both as to tumors and cells, persists. Heterologous transplantations of such tumors have not been reported.

The age factor in transmissible tumors is less a definitive property than race. But the age of animals undoubtedly affects their susceptibility to certain tumors. The Murray-Begg endothelioma with which I worked would take in 100 per cent of young Rhode Island Red chicks. As the animals reached maturity the proportion fell off until an age was reached when only about 10 per cent of the chickens were susceptible. It is common practice in laboratories where, particularly, chicken sarcomas are being studied to discard chickens when they reach five to six months of age, as then takes are not regular nor constant. This age corresponds with the period of sexual maturity in most chickens. On the other hand, spontaneous or transmissible *carcinomas* usually occur in older animals. For instance, the Buffalo strain of mice develop tumors on an average at eighteen months of age; the youngest to acquire a tumor was five months old. These tumors, therefore, follow the natural laws which control, more or less, the growth of human tumors and, to a considerable extent, normal tissues.

SIMILARITY OF HUMAN TUMORS TO THOSE OF LOWER ANIMALS

Factors entering into tumor susceptibility in man are less well defined, because of lack of complete knowledge of genealogy. There is, therefore, more dispute concerning hereditary susceptibility or immunity of man to tumors than of animals. But considerable evidence has accumulated to show that, at least in some lines of descent, tumor susceptibility may be inherited. Warthin's [6] cancer families are striking examples. In these a large proportion of several generations contracted carcinomas. The finding of papillo-

mata of the colon in successive generations of a family has been described by Dukes.[7] It is common knowledge that angiomas of the skin may be "inherited," and that pigmented moles run in families. Sometimes these tumors occur in exactly the same parts of the body through several generations.

That there is a racial tendency to some forms of tumors there appears to be no doubt. Naevi are more common in darker individuals. Strangely enough these tumors rarely become malignant in the more pigmented strains. Melanotic sarcomas and carcinomas are much more common in the light-skinned. This is analogous, again, to lower animal tumors. Black horses rarely, if ever, develop melanomas; light or gray horses are much more susceptible. The overproduction of fibrous tissue in the negro is an illustration of the tendency in this race to fibrous tissue tumors. The production of large keloids following injury, sometimes used as facial or body ornamentation, is common to the negro, and seldom occurs in the whites. Fibrosarcomas of low malignancy occur in the extremities of negroes much more commonly than in others. The frequency of fibromyomas in this race is likewise common knowledge. On the other hand, epidermoid carcinomas, of the skin particularly, are quite uncommon in negroes.

TRANSPLANTATION OF HUMAN TUMORS

One may think of malignant tumors in man as coming under two general classes: one, malignant because of an innate biological change in the cell so that the name "virulent" might properly be applied to it; and a second, which consists of viable cells capable of growing locally or in remote places when transported there. This second group may be called malignant by accident. The first are the usual carcinomas and sarcomas which actively invade normal tissues, metastasize widely, and consist of greatly anaplastic cells with all the changes characteristic of malignant growths. The second comprise those tumors which we look upon as "locally malignant" or which may be transplanted, but rarely metastasize. There are typical members of each group, but the line of demarcation between some of them is not sharp. The first group corresponds roughly with spontaneous malignant (inoculable) tumors in animals; the second, with artificial tumors (transplantable) as previously defined (not tar cancers and similar tumors).

Examples of the second group are many. The embryonal fibrosarcoma of children consist of undifferentiated mesenchymal tissue which forms both connective tissue and thin-walled vascular channels. This tumor grows slowly, infiltrates moderately, but usually does not metastasize. It frequently recurs after excision. It would probably transplant readily to another child. Such a tumor corresponds to the transplantable tumors produced in animals by engrafting embryonic tissue. The cells simply have the ability to grow so long as ample nourishment is provided, and, in a sense, have no malignant intention. Other examples are adamatinomas, chordomas, "mixed" tumors of the parotid, and, in a less degree, basal celled epitheliomata.

Tumors in the human which transplant themselves without actively metastasizing are best illustrated by the papillary adenocystomas of the ovary. These may be regarded as fairly safe tumors until they rupture. When spilled into the peritoneal cavity, however, the cells of the tumor have the property of continued growth, and may prove to be malignant "by accident." That normal tissue may behave in exactly the same way has been shown by Sampson and by Jacobson in the case of endometrial transplants. This misplaced tissue continues to grow, and is entirely similar to a locally malignant tumor in its behavior.

Naturally, deliberate attempts to transplant tumors from man to man are not numerous. Coca [8] records the autotransplantation of cancer into the abdominal wall from the use of ground-up cancer tissue (Coca and Gilman's "vaccine"), and Coffey [9] records three others. Cornil [10] mentions the successful grafting of a sarcoma and an adenocarcinoma to other parts of the same persons bearing them. Hahn grafted [11] an epidermoid carcinoma from one portion of the body to another. Among those cases treated with fresh or phenolized tumor emulsion there were some injected with tumor tissue from other individuals. There are no reports, however, of such transplants growing.

SPONTANEOUS RETROGRESSION OF TUMORS AND IMMUNITY

Transmissible tumors of rats, mice, chickens, and other animals occasionally undergo spontaneous retrogression. In the case of chicken sarcomas this usually occurs in older animals, and as suggested previously, this may be influenced by the ripening of the sex glands. In most of these animals the tumor will grow for a while, remain inactive for a period, and then slowly regress and disappear. Similar occurrences are found in the case of human tumors. Cases are reported by Rotter [12] (carcinomas of the rectum), Senger [13] (carcinoma of the mouth), Crosbie [14] (lip), and Gaylord and Clowes [15] (chorion epitheliomas). Flesch [16] reported a huge ovarian carcinoma with metastases which disappeared. Wells [17] mentions a case in which there was spontaneous disappearance of a carcinoma of the colon which reappeared fifteen years later. Similar cases are being mentioned in current literature, but one must be exceedingly critical of many of them. There are enough authentic cases, however, to prove the exception. That some systemic factor or factors develop in such individuals and do not in others (but *are* present in totally immune persons) there can be no doubt. There is not enough evidence to prove that purely local causes are responsible for all these cases. Whether it is possible to transmit those factors to other more susceptible individuals remains to be seen. If they are entirely hereditary or racial in character, the chance for a systemic treatment for cancers

seems far remote. Active immunization against experimental tumors has been claimed by Stickler [18] and others, but this immunity could not be transmitted passively to another animal.

FACTORS WHICH ALTER THE RATE OF GROWTH OR SUSCEPTIBILITY TO TUMORS

That tumor growth may be affected by various conditions, natural and artificial, has been shown by both clinical observation and experiment. The rapid growth of tumors of the breast during the period of lactation, as opposed to that in the inactive breast, is a striking illustration of the presence of a growth-promoting substance. That this is not entirely due to an increased blood supply is shown by the more rapid growth of breast carcinomas generally in young sexually mature women in the absence of lactation. The so-called "inflammatory cancer" of Handley may cause death from widespread metastases in as short a period as six weeks, and these occur only in young women, most of whom have not been pregnant.

Many artificial methods have been used in attempts to alter the growth of tumors. Excluding actual destructive agents (x-ray, radium, corrosives, the cautery) their number and variety are legion. Any protein or colloidal solution may affect some tumors, perhaps most frequently causing an acceleration of growth with consequent necrosis, and so producing a false impression of benefit. Glandular extracts of many kinds (thyroid, thymus, pituitary, adrenal, spleen, and others) have been used, mostly without effect. But I wish to show how some manipulations may alter to at least a slight degree the progress of tumors, modify their usual course, or sometimes cause complete retrogression. If it were not for these isolated instances of apparent effect, one would be entirely justified in declaring that any attempt to treat tumors, now or in the future, as systemic diseases capable of being influenced in any way by chemical factors would be hopeless, unwarranted, or even absurd.

Space does not permit detailing even a small proportion of the experiments which have in some way modified tumor growth or susceptibility. For the sake of brevity, the following instances are merely catalogued to point out the many trends which research has taken.*

Removal of the spleen seems to make some animals more susceptible to tumors (Murphy [19] Peracchia and Castellano [20]).

Parathyroid hormone caused rat tumors to grow more rapidly than in controls (Goerner and Shafiroff [21]).

A diet deficient in potassium caused a retardation in growth of mouse sarcomas, and complete retrogression in some (Langfeldt [22]).

Insulin caused a more rapid growth in transplanted rat sarcomas (Barral and Cade [23]).

A diet deficient in vitamin B causes a retardation in the growth of tumors (Caspari and Ottensooser [24]).

Thyroid extract causes an acceleration of the growth of tumors (Flaks [25]).

Adrenalin causes a more rapid growth of cancer cells (Baroni [26]).

Adrenal cortical extracts have no effect on the longevity of chickens suffering from a fibrosarcoma (Connor [27]).

Thymus extract has little or no effect on tumor growth, behaving as a foreign protein (Elsner [28]).

Decreased atmospheric pressure caused a high percentage of retrogressions in rat sarcomas (Sundstroem [29]).

One could continue indefinitely enumerating methods or substances which modify in some way the growth of tumors. With the exception of the experiments reported by Sundstroem, some cases treated with colloidal lead, and the rare cases reported by Coley in which his mixed toxins were used, practically no cures have resulted from this great mass of experimental work. But it shows what I am trying to point out that the life history of many tumors *can* be modified, they *can* be made to grow faster, or slower, and in a few cases *can* be made to disappear. The wide variety of methods used, the number of different species of animals studied, and the variation in types of tumors which are affected in different ways by the same substances, indicate also that probably no single substance or method will ever be found that will act the same way on all tumors. But these very facts indicate that fundamental research in cancer is now more important than ever, and that though a critical, even skeptical, attitude must be maintained in regard to all phases of work on tumors, complete and abject submission to an almost insurmountable problem is not necessary.

* For a good review of this subject, see Woglom, Cancer Review, IV, 129, 1929.

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DISCUSSION

HOWARD O. BALL, M. D. (The W. K. Kellogg Foundation, Los Angeles).—This paper points out very aptly many of the difficult and only partially solved problems connected with the study of malignant tumors, clinically or experimentally. The questions of *how* and *why* for even the observations presented here remain largely unanswered. Species specificity for transplantable tumors is no longer specific. German workers have recently recorded the transplantation of a human tumor (carcinoma of cervix) to white mice.

I heartily agree with Doctor Connor that a great need for fundamental laboratory work exists; and an important field, I think, is chemistry. We need more specific reactions for organic substances when present in small amounts in tissues or body fluids. We need histochemical reactions in the microscopic study of cancer tissues, and cancer cells. The explanation of many of the problems of the transmissibility, and possibly even of the hereditary susceptibility of malignant tumors, may finally be chemical. Such a knowledge would help us better to interpret the exceptions which exist. It would certainly indicate whether malignant diseases should be considered as having a common etiology, and thus whether any single procedure could ever be reasonably expected to modify the course or exterminate the existence of a malignant process.

Every present-day method of treating malignant diseases is empirical. Rational therapy can only follow more knowledge of a fundamental character, particularly as regards etiology.

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H. J. ULLMANN, M. D. (Santa Barbara Cottage Hospital, Santa Barbara).—Doctor Connor's paper when published will be of great value as a reference work to all those doing research in cancer. It should be read by all surgeons, radiologists, and clinicians, who are dealing with cancer, so that they may think with knowledge and not become too enthusiastic over the regression of a few tumors following the use of any new method of treatment. It is only by the observation of large numbers of tumors in comparison with controls that any method of treatment can be properly evaluated. I was much interested in the suggestion that the increased necrosis or a liquefaction of some tumors following the injection of various substances might be due to an acceleration of growth with choking off of the blood supply, rather than a direct effect on the tumor tissue itself. This is undoubtedly a factor or possibility that must be taken into consideration. We have lately been able to study such effects. Bischoff and Maxwell, in our laboratories, have found that the Allan-Doisy follicular preparation, corpus luteum extract, and four adrenal extracts, when injected subcutaneously into rats, brought about an early instance of liquefaction or opening of R-10 sarcoma without effecting the incidence of regression.

I do not believe it possible, on the basis of our present knowledge of cancer, that any single substance or method of treatment will ever be found that may be used for all types of malignancy. To me it is as absurd to look for a single cancer cure or treatment as it is to look for a single cure or treatment for "infectious disease." And the treatment of all forms of malignancy by one method is equivalent to treating such infections as malaria, syphilis, and pneumonic plague, with the same remedies and procedures.

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W. T. CUMMINS, M. D. (Southern Pacific General Hospital, San Francisco).—The world's major medical subject appears undeniably to be a biochemical problem. Each of the main types of spontaneously developing malignant tumors may be caused by a specific, and possibly widely different, pathologic metabolic product, or group of products. The subject of immunity and susceptibility in lower animals, as well as in human beings, is as conspicuous in the problem of neoplastic study as it is in infectious diseases. Spontaneous retrogression and disappearance of neoplasms and their retrogression, in consequence of protein inoculation, are subjects of great interest.

Exhaustive studies of histochemical conditions in normal, abnormal non-neoplastic and neoplastic tissues may illuminate the subject. This work is being carried out apparently by a very limited number of investigators.

The topic presented by Doctor Connor has been elaborated most interestingly and well, with the presentation of the facts and of the problems that confront the investigator.

To the progressively increasing army of workers throughout the world, there must be added a host, all of whom, well trained, must attack the neoplastic problem for its final subjugation.

TRICHORRHEXIS NODOSA—A CLINICAL PROBLEM*

REPORT OF CASES

By CHARLES R. CASKEY, M. D.
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DISCUSSION *by Stanley O. Chambers, M. D., Los Angeles; Hiram E. Miller, M. D., San Francisco; H. J. Templeton, M. D., Oakland.*

IT was with considerable hesitancy that I decided to write upon a subject about which so little is known. However, having observed twelve cases of a supposedly rare condition during the past year and having made some observations on the course and treatment of a few of them, I deem it worth while to report these cases at this time. If this incomplete report stimulates further study its aim will have been attained.

In order to obviate any confusion that may exist on the part of my hearers concerning the nomenclature of the subject of this essay, the following terms are defined: Trichorrhexis nodosa, as the name implies, is characterized by the presence on the shaft of the hair of one or more irregularly spaced, small, grayish nodes. Microscopically, these nodes at that point show longitudinal splitting of the hair, resembling two small paint brushes jammed end to end. Trichoclasia, essentially a later stage of trichorrhexis nodosa, is the transverse fracture of the shaft of the hair at the middle of the node from traction or bending, while trichoptilosis designates a longitudinal splitting of the shaft of the hair into two or more fibrils.

* Read before the Dermatology and Syphilology Section of the California Medical Association at the fifty-ninth annual session at Del Monte, April 28 to May 1, 1930.